REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Following the amendments, claims 21, 25-29, 33, 36, 37, 41, 43, 47-53, and 57-60 are under consideration, with claims 21 and 57 being in independent format.

Upon review of the Office Action of June 26, 2006, applicant's representative noted that the amendment submitted on May 3, 2006, did not appear to have been entered. In a telephone call with Examiner Kwon on September 20, 2006, applicant's representative was advised that it is not necessary to resubmit the amendment dated May 3, 2006. Entry and consideration of that amendment is respectively requested.

Applicant notes that the Examiner has not yet examined claim 57, added in the amendment dated May 3, 2006. It is therefore submitted that, if the Examiner rejects this claim in the next Office Action, the Office Action should not be made final.

Applicant affirms the election of claims directed to methods for treating headaches and symptoms of migraine headaches by administering compositions comprising $Na^+K^+2CL^-$ cotransporter antagonists (claims 21, 25-29, 33, 36, 37, 41, 43, 47-53 and 57) in response to the Restriction Requirement. The Examiner indicates that claims 45 and 47-53 are withdrawn following the Restriction Requirement. However, applicant notes that in the amendment mailed May 3, 2006, claims 47-53 were amended to remove reference to non-elected claim 45 and therefore should not have been withdrawn. Consideration of claims 47-53, together with claim 57 added in the amendment of May 3, 2006, is respectively requested.

Claims 58 and 59, which recite a method of claim 57 wherein the $Na^+K^+2CL^-$ cotransporter antagonist is furosemide or bumetanide, respectively, have been added. Newly added claim 60 recites subject matter previously recited in claim 27, namely the method of claim 21 wherein the $Na^+K^+2CL^-$ cotransporter antagonist is bumetanide. Claim 27 has been amended to remove the phrase "furosemide-related compositions" and to remove reference to bumetanide. Claims 25, 26 and 27 have been amended to clarify that the blood brain barrier permeability enhancer, hyperosmotic agent anticonvulsant and/or non-steroidal anti-inflammatory drug is administered in a separate step to the $Na^+K^+2CL^-$ cotransporter antagonist. In addition, claims 27 and 48-53 have been amended to correct a typographical error.

It is urged that support for these amendments may be found throughout the specification as originally filed and that none of the amendments constitute new matter or raise new issues for consideration.

Claim Rejections – 35 USC §112, first paragraph, enablement

Claims 21, 25-29, 33, 36, 37, 41 and 43 stand rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure. Specifically, the Examiner asserts that the application is only enabling for the use of furosemide and not for the use of any other $Na^+K^+2CL^-$ cotransporter antagonists. Applicant strenuously disagrees with the Examiner's position and respectfully traverses this rejection.

Independent claim 21 is drawn to methods of treating migraine headaches and the symptoms of migraine headaches by administering a composition, wherein the composition consists essentially of a $Na^+K^+2Cl^-$ cotransporter antagonist that is capable of inhibiting $Na^+K^+2Cl^-$ transport in glial cells, i.e. wherein the only active agent in the composition is the $Na^+K^+2Cl^-$ cotransporter antagonist. Dependent claim 27 is drawn to such methods wherein the composition is either furosemide or bumetanide. Independent claim 57 is drawn to methods for treating migraine headaches and symptoms of migraine headaches, wherein the method consists essentially of administering a $Na^+K^+2Cl^-$ cotransporter antagonist that is capable of inhibiting $Na^+K^+2Cl^-$ transport in glial cells, i.e. wherein the only therapeutic step is the administration of the $Na^+K^+2Cl^-$ cotransporter antagonist.

The specification presents studies demonstrating that furosemide is effective in blocking epileptiform activity and in dissociating synaptic synchronization, both *in vitro* and in an animal model (see Examples 1-3, pages page 24, line 27 – page 30, line 18). Furthermore, as taught in the specification (for example at page 46, lines 17-20, and page 9, line 32, - page 10, line 26), applicant has determined that $Na^+K^+2Cl^-$ cotransporter antagonists, such as furosemide and bumetanide, are able to desynchronize neuronal activity without reducing excitability and that it is this ability to reduce hypersynchronization of neuronal population activity that enables $Na^+K^+2Cl^-$ cotransporter antagonists to be effective in treating disorders such as epilepsy and migraine.

As demonstrated by Declaration of Dr. John Partridge, submitted herewith, one of skill in

the art would appreciate that bumetanide and furosemide have similar chemical structures and based on those similarities, would reasonably expect them to have similar functional properties. This is further supported by the studies described in Schwartzkroin et al., *Epilepsy Research* 32:275-285, 1998 (copy enclosed for the Examiner's convenience), which show that both furosemide and bumetanide are effective in blocking epileptiform activity.

It is thus urged that, on being provided with the instant specification, one of skill in the art would be able to practice the presently claimed methods with a reasonable expectation of success, and the present rejection of claims 21, 25-29, 33, 36, 37, 41 and 43 under 35 USC §112, first paragraph, may be properly withdrawn.

Claim Rejections – 35 USC §112, second paragraph

Claims 21 and 25-27 stand rejected under 35 USC §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The Examiner has objected to the recitation of "a blood brain barrier permeability enhancer" and "a hyperosmotic agent" in claims 25 and 26, respectively, on the basis that "the specification does not define the terms". It is submitted that both of these are terms that are well understood by those of skill in the art to have specific meanings and therefore it is not necessary for the specification to define these terms. Support for the applicant's position with regards to the phrase "blood brain barrier permeability enhancer" is provided, for example, by Liu et al., *J. Pharmacol. Exp. Ther.* 2006 Jun 27 [Epub ahead of print], and Witt et al., *Peptides 22*:2329-43, 2001. Support for applicant's position with regards to the phrase "hyperosmotic agent" is provided, for example, by Bermueller et al. *J. Neurol. Sci. 241*:73-82, 2006, and by Jansen et al., *J. Biomed. Opt. 11*:041119, 2006. Copies of the abstract for these articles are submitted herewith for the Examiner's convenience. Applicant further notes that the Patent Office has previously issued several patents wherein the phrase "hyperosmotic agent" appears in the issued claims including, for example, US 7,037,895 issued May 2, 2006, and US 6,942,663 issued September 13, 2005.

With regards to claim 27, the Examiner states the term "furosemide-related compositions" renders this claim indefinite. While the applicant does not agree with the Examiner's position, this phrase has been cancelled from claim 27 in order to expedite allowance

of claims to subject matter currently of most interest to the assignee of record.

The Examiner has objected to claim 21 due to the recitation of the phrase "consisting essentially of", on the basis that dependent claims 28 and 29 "allow for the inclusion of other active ingredients such as anticonvulsant and non-steroidal anti-inflammatory drugs that are know to treat migraine headaches and symptoms of migraine headaches". Applicant respectively submits that claim 28 is *not* directed to methods comprising administering a single composition including both a $Na^+K^+2Cl^-$ cotransporter antagonist plus an anticonvulsant and/or a non-steroidal anti-inflammatory drug, but rather to a method comprising the step of administering a composition consisting essentially of a $Na^+K^+2Cl^-$ cotransporter antagonist and, *in a separate step*, administering an anticonvulsant and/or a non-steroidal anti-inflammatory drug. Claim 28 has been amended to clarify this.

It is respectfully submitted that one of skill in the art would clearly be able to determine the metes and bounds of all the presently pending claims and that this rejection of claims 21 and 25-27 under 35 USC §112, second paragraph, may thus be properly withdrawn.

Claim Rejections – 35 USC §103

Claims 21, 25-29, 33, 36, 37, 41 and 43 stand rejected under 35 USC 103(a) as being unpatentable over Read et al. (Cephalalgia, December 1997, 17:826-832) in view of Mathew et al. (Neurology, 1996, 46:1226-1230), Levin (US 6,432,986), Bentley et al. (US 6,369,094) and Becker (US 5,256,687). This rejection is respectfully traversed.

The Examiner asserts that Read teaches the use of furosemide in inhibiting regenerative cortical spreading depression in anaesthetized cats and also teaches that the inhibition of cortical spreading depression is *potentially* useful for the treatment of migraine therapy (emphasis added). As discussed in the Amendment and Reply filed on November 24, 2004, applicant's research indicates that the December 1997 issue of Cephalalgia was not received by any subscriber on or before the December 23, 1997, priority date of the present application, and that the Read et al. reference is therefore **not** prior art to the present application. Applicant notes that the courts have held that there can be no rejection under 35 USC §102(a) if there is no proof that a reference was accessible to any member of the public prior to the filing date of an application

(Carella v. Starlight Archery 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); see MPEP 2128). It is therefore submits that there is no proof that the Read et al. reference was available to any subscriber before the priority date of December 23, 1997, and that Read et al. therefore cannot be applied as a §103/102(a) prior art reference. Applicant notes that this information has been submitted to the Examiner previously and requests that the Examiner specifically responds to the applicant's position on this matter.

Even if further investigation were to show that selected subscribers *did* receive the December 1997 issue of Cephalalgia prior to the December 23, 1997, priority date, it is submitted that the teachings of Read et al. would not have rendered the present invention obvious. Read et al. present experimental data showing that furosemide inhibits regenerative cortical spreading depression (CSD) in anaesthetized cats, and speculate that compounds with the ability to modify CSD *may* have potential as anti-migraine compounds. While one of skill in the art, at the time the application was filed, *might* have been motivated to combine the teachings of Mathew et al. with those of Read et al., applicant submits that the combined teachings would not have led one of skill in the art to reasonably believe that furosemide *alone* could be *successfully* employed in the treatment of migraine. It was not until applicant's elucidation of the role of $Na^+K^+2Cl^-$ cotransporter antagonists in modulating (reducing) the synchronization of neuronal population activity that is associated with seizure disorders and migraine headaches, that one of ordinary skill in the art would have had any reasonable expectation of success in employing $Na^+K^+2Cl^-$ cotransporter antagonists, such as furosemide, in the treatment of migraine headaches and symptoms. Furthermore, as evidenced by Ebersberger et al. (Ann. Neurol. 49:7-13, 2001; copy enclosed for the Examiner's convenience), there was still considerable debate among the scientific community as to whether or not CSD was related to migraine several years **after** the priority of the present application. Applicant thus submits that, at the priority, or even the filing, date of the present application one of skill in the art, in view of the cited prior art references, would not have been able to use $Na^+K^+2Cl^-$ cotransporter antagonists to treat migraine with a reasonable expectation of success.

The Examiner states that "Mathew is being supplied as a reference to demonstrate the use of nonsteroidal anti-inflammatory agent, abortive antimigraine agents (e.g. ergotamine, DHE, or

sumatriptan), beta blockers, amitriptyline, and/or methysergide in combination of furosemide for the treatment of chronic daily headache including migraine headache with or without aura in human". It thus appears that the Examiner is *not* applying Mathew et al. against at least claims 21, 25, 27, 36, 37, 41 and 43.

Mathew et al. describe studies in which administration of a combination of both furosemide and acetazolamide together with known anti-migraine agents lead to improved control of symptoms in a subset of patients with refractory transformed migraine type of chronic daily headache (CDH) who had also been identified as having increased intracranial pressure (also referred to as idiopathic intracranial hypertension or IIH). Mathew et al. conclude that their observations indicate a *possible* link between migraine and IIH. Mathew et al. do not teach or suggest that administration of furosemide and/or acetazolomide in the absence of conventional anti-migraine agents would be effective in relieving the symptoms of migraine. Nor does Mathew et al. overcome the deficiencies of Read et al. discussed above.

The Examiner states that Levin and Bentley et al. demonstrate the routine knowledge in the art of various methods of delivery, formulations and dosage forms for anti-migraine agents, and further that Becker et al. demonstrates the routine knowledge in the art of using mannnitol as a carrier for furosemide. However none of these references overcome the deficiencies of Read et al. discussed above.

It is submitted that neither Read et al., Mathew et al., Levin, Bentley et al. nor Becker et al., taken either singly or in combination, would have rendered the presently claimed methods obvious to one of skill in the art at the time the application was filed, and that the rejection of claims 21, 25-29, 33, 36, 37, 41 and 43 under 35 USC §103(a) may thus be properly withdrawn

Conclusion

Every effort has been made to put the claims in condition for allowance. Early reconsideration and allowance of the pending claims is respectfully requested. If the Examiner has any further concerns regarding the application, he is invited to telephone the undersigned at 206.382.1191.

Charge Deposit Account

Please charge any additional fees that may be required, or credit any overpayment, to our Deposit Account No. 19-3555.

Respectfully submitted,

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Date: September 27, 2006

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